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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/965,356	11/06/97	BERNFIELD M	CMCC533

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EXAMINER	
BAKER, A	
ART UNIT	**PAPER NUMBER**
1632	24

DATE MAILED: 02/01/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/965,356	Bernfield et al.
Examiner	**Group Art Unit**
Anne-Marie Baker, Ph.D.	1632

☒ Responsive to communication(s) filed on *Jan 7, 2000*.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1, 3-6, 10, and 12-15* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 3-6, 10, and 12-15* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The amendment filed January 7, 2000 (Paper No. 20) has been entered. Claims 1, 3-6, 10, and 13-15 have been amended. Claims 2, 7-9, and 11 have been cancelled.

Claims 1, 3-6, 10, and 12-15 are pending in the instant application.

The request filed on January 7, 2000 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/965,356 is acceptable and a CPA has been established. An action on the CPA follows.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-6, 10, and 12-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse having a genome comprising a stably integrated DNA sequence encoding a syndecan operably linked to a promoter, wherein expression of the DNA sequence results in the mouse developing maturity onset obesity and methods of using said mice, does not reasonably provide enablement for any transgenic rodent expressing a syndecan from a transgene construct. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1 and 3-6 are drawn to a transgenic rodent whose genome comprises a stably integrated DNA sequence encoding a syndecan operably linked to a promoter, wherein expression of the DNA sequence results in the rodent developing maturity onset obesity. Claims 10 and 12-15 are drawn to methods for screening for compounds which can alter body weight.

The specification fails to provide an enabling disclosure for the preparation and use of any transgenic rodent having a syndecan gene integrated into the genome such that syndecan is expressed from a heterologous construct, because no guidance is provided in the specification fro the preparation and use of any transgenic rodent other than mice. The claims encompass any rodent having a syndecan transgene, but the specification is enabling only for mice. As discussed herein below and in the previous Office Actions (Paper Nos. 8 and 13), phenotypic alterations resulting from the introduction of a transgene into an animal's genome cannot be predicted, even when the function of the gene is known. Thus the model system of Claims 10-15, wherein the transgenic rodents are useful for the screening of compounds which can alter body weight is enabled only for transgenic mice expressing a syndecan transgene of the type disclosed in the specification. The phenotype of any other transgenic rodent expressing an exogenous syndecan cannot be predicted and has not been demonstrated.

The specification fails to provide an enabling disclosure for the preparation of any species of transgenic rodent of the type claimed because the phenotype of a transgenic animal cannot be predicted. In the absence of a transgene-dependent phenotype, one skilled in the art would not know how to use the claimed animals. The phenotype of any species of rodent expressing a syndecan-encoding transgene as recited in the claims, cannot be predicted. The specification does not teach what phenotype would be observed in any species of transgenic rodent of the type claimed other than the mouse. Furthermore, the specification does not adequately teach how one would have prepared any and all transgenic rodents expressing a syndecan-

encoding transgene, because the specification does not teach constructs with appropriate regulatory regions that would work in any rodent, thereby imparting an obese phenotype to the resultant transgenic animal. The mere capability to perform gene transfer in any given species is not enabling for the claimed transgenic rodents because a predictable phenotype cannot be achieved by simply introducing a transgene encoding a gene of interest. While gene transfer techniques are well-developed for a number of species, especially in the mouse, methods for achieving the desired level of transgene expression in appropriate tissues are less well-established. The introduction of DNA into the mammalian genome can ordinarily be achieved most reliably by microinjection or retrovirus-mediated gene transfer. However, the state of the art for transgenics is unpredictable because the method of gene transfer typically relies on random integration of the transgene construct. Insertional inactivation of endogenous genes and position effects (see Wall, 1996, p. 61, paragraph 3) can dramatically influence the phenotype of the resultant transgenic animal. Integration of the transgene near highly active genes or, alternatively, in a transcriptionally inactive region, can influence its level of expression. Furthermore, expression of the transgene and the effect of transgene expression on the phenotype of the transgenic animal depends on the particular gene construct used, to an unpredictable extent. The particular genetic elements required for appropriate expression varies from species to species. Thus, a construct that confers the desired phenotype in a mouse will not necessarily achieve the same result in a rat. Wall (1996) reports that our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (p. 61, paragraph 3). This is especially relevant for species in which genetic studies are less advanced than in the mouse. Thus, the species-specific requirements for transgene design introduces an additional level of unpredictability associated with the development of transgenic animals. Furthermore, there are inherent physiological differences between mice, rats, and other rodents that can affect the phenotype in an unpredictable manner. In the absence of representative working

examples, the existence of any phenotypic alteration resulting from the introduction of a syndecan-encoding transgene in any rodent species, is highly unpredictable. Without knowing the phenotype of the transgenic rodent, one of skill in the art would not know how to use the animal. Given the lack of working examples, the limited guidance in the specification, and the unpredictability in the art, one of ordinary skill in the art would have been required to engage in undue experimentation in order to make and use the full scope of the claimed transgenic rodents.

While the species-specific requirements for transgene design are not clearly understood, examples in the literature demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins et al., 1990 produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer et al., 1990 describe spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice (Mullins et al., 1989; Taurog et al., 1988) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats.

Given that specific phenotypic alterations cannot be predictably achieved by merely transferring a gene of interest into an animal, specific guidance must be provided to enable the instant invention. The specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. The claims cover any species of transgenic rodent having a syndecan-encoding transgene, but the specification does not enable the full scope of the claimed animals. In the absence of disclosure of transgenic rodents, exhibiting a transgene-dependent phenotype, representative of the

full scope of the claimed transgenic animals, undue experimentation would have been required to make and use the claimed animals.

The specification fails to provide an enabling disclosure for the preparation of any transgenic rodents carrying a syndecan-encoding transgene construct other than mice. The specification describes the preparation of mice expressing a transgene construct comprising a nucleic acid molecule encoding syndecan-1 operably linked to the CMV promoter/enhancer regulatory regions, wherein expression of the transgene results in mice that exhibit maturity onset obesity. Syndecans have been identified in the mouse, rat, hamster, and human. However, other animals for which syndecans have not been identified, or for which the gene for a syndecan is not known, are not enabled for the generation of transgenics that overexpress a syndecan transgene. Furthermore, phenotypic alterations resulting from the introduction of transgenes is highly unpredictable. Given the lack of any demonstration of a maturity onset obesity resulting from expression of a syndecan transgene in any rodent other than the mouse and given the unpredictability of obtaining a specific phenotypic alteration as the result of the introduction of a defined transgene construct, one skilled in the art would have been required to have exercised undue experimentation to have practiced the invention in any animal other than the mouse. Thus, limitation to mice carrying the claimed transgene construct is appropriate.

Applicants argue that four of the publications relied on in the enablement rejection do not indicate unpredictability in the art, but rather support the claimed subject matter. Specifically, Applicants point out that Taurog et al. (1988) disclose transgenic mice that express human HLA-B27 at significant levels and that Hammer et al. (1990) disclose transgenic rats that express human HLA-B27. Applicants further point out that Mullins et al. (1989) disclose transgenic mice that express the Ren-2 gene product and that Mullins et al. (1990) discloses transgenic rats that express the Ren-2 gene product. Applicants argue that expression alone

is testament to the power of transgenic technology. However, the enablement rejection is based on the unpredictability of phenotype. The effect of transgene expression is unpredictable as indicated by the cited references. Thus, while some level of expression may be seen in both rats and mice, the effect of that expression produces widely varying results. Transgenic mice expressing Ren-2 do not exhibit hypertension, whereas Ren-2 transgenic rats do. The instantly claimed invention encompasses transgenic rats that express a syndecan transgene and exhibit maturity onset obesity as a result. Given the state of the art, the phenotype of a syndecan transgenic rat is unpredictable. Applicants argue that the cited references support the assertion that transgenic expression is expected within any species of the genus of rodents when the transgenic version of one species, mouse, has been shown to express the desired transgene product. However, the effect of transgene expression (i.e. the phenotype) is unpredictable, as exemplified in the cited references.

Applicants argue that the mouse/rat transgene combination reported in Mullins 1 and Mullins 2 indicates the strong predictability of transgenic technology. However, although the Ren-2 transgene produced hypertension in rats, it did not produce the same effect in mice. Thus, the result produced in one species of rodent is not predictive for another rodent species. Accordingly, undue experimentation would have been required to produce transgenic rats exhibiting maturity onset obesity as a consequence of expression of a transgene construct of the type recited in the claims.

Applicants further argue that mouse promoters work in rats and that this is evidence of the predictability of transgenic activity. However, even if predictable levels of expression were obtainable in all rodent species, the effect of transgene expression is still not predictable. For example, even if one could design a transgene construct that would produce a desired level of expression of a syndecan in a transgenic rat, the instant specification does not disclose the level of expression of any syndecan that would be required in a rat or other rodent to produce a phenotype of maturity onset obesity. Undue experimentation would have

been required for one skilled in the art to make the full scope of the claimed rodents with maturity onset obesity.

Applicants argue that once constructs and transgene units developed for transgene implantation in one species within the genus rodents are shown to function, other transgenic species within the genus can be made without undue burden or experimentation. However, transgenes that function in the same manner in multiple rodent species, wherein said function is sufficiently similar to produce the same biological effect, are inherently unpredictable, for the reasons discussed above. It is not enough to produce any level of transgene expression, even so-called "significant" levels, because the level of expression sufficient to produce the desired phenotype is not known. Undue experimentation would have been required for one skilled in the art to determine the level of expression required and to design appropriate transgene constructs that would produce the required level of product.

Applicants argue that the procedure for producing transgenic rats was essentially the same as the procedure for producing transgenic mice. The methodology for producing transgenic rodents is not an issue in the rejection. The enablement rejection is based on the unpredictability of using transgenic technology to produce a defined phenotype in any rodent species. Applicants argue that once the first transgenic rodent for a particular species is made, the techniques developed for that transgenic rodent are applicable to other rodent species. The cited references refute this argument.

Applicant is advised that the disclosed transgenic mouse with a syndecan-1 gene operably linked to regulatory regions that drive expression of the transgene such that the mouse exhibits maturity onset obesity is enabled by the specification but not expressly claimed as such. The assay for screening compounds which can alter body weight is also enabled for the same scope as the animals. Claims limited to transgenic mice

carrying a transgene construct of the type disclosed, wherein the mice exhibit the disclosed phenotype are appropriate.

Conclusion

No claim is allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on (703) 308-2035. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Anne-Marie Baker, Ph.D.

Jasemine C. Chambers

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